

## **REMARKS**

### **Status of the Claims**

Claims 1-7 were previously presented for examination, and were rejected. Claim 2 has been canceled; claims 1 and 3-7 have been amended; and a new claim 8 has been added. Support for the amendments may be found, *inter alia*, at paragraphs [0005] and [0014]-[0016] of the specification as filed, in Figures 1-5 and in original claims 2 and 6. Thus, no new matter has been added by way of these amendments. Upon entry of the amendments, claims 1 and 3-8 will be pending. Entry of the amendments and reconsideration in view of the following comments is respectfully requested.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

### **Rejection under 35 U.S.C. § 102**

Claims 1-3 and 6-7 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Zhao et al. (US 6,939,451 B2) (“Zhao”).

The Examiner alleged that Zhao discloses a capillary electrophoresis chip apparatus comprising an electrophoresis chip having an upper planar substrate having one or more microchannels and one or more apertures for loading samples; a middle electrode layer that bonds to the bottom of the substrate enclosing and sealing the microchannels to form an intact capillary and providing the voltage for electrophoresis; and a lower heating layer wherein the individual layers are thermal conductive and adhesive to each other. Further, the Examiner asserted that Zhao discloses a one-dimensional microchannel and the “possibility” of multidimensional microchannels. Finally, the Examiner alleged that Zhao teaches a heating layer comprising heaters placed within certain localized regions along the microchannels, and argued that a skilled artisan would appreciate

that the heating layer of Zhao would be capable of providing a stable temperature gradient (the OA at pages 2-3). Applicants respectfully traverse this rejection.

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597 (Fed. Cir. 2002). To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. *In re Paulson*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (citing *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990)). “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131.

As a preliminary matter, claim 1 as amended recites, *inter alia*, an upper channel layer comprising a two-dimensional or multidimensional microfluid channel and a lower heating layer capable of providing a stable temperature gradient for electrophoresis comprising two or more sets of temperature control elements that are spaced apart from each other (emphasis added).

Zhao teaches a microfluidic chip comprising a substrate having interconnected micro-channels and one or more apertures, with a cover bonded to the substrate to enclose the microchannels and form a reservoir at the aperture (col. 2, lines 19-21). Zhao also teaches chip configurations further comprising integrated electrode heating components (col. 12, line 62 – col. 13, line 67; FIGS. 6-9). Zhao teaches that the heating components are intended to control the temperature in a microfluidic channel and can have a form of a solid band, a serpentine-like heater element, or a variation thereof (col. 13, lines 44-52 and 63-67).

Zhao does not teach that the disclosed microfluidic chip may be used for detecting a nucleotide polymorphism or a single nucleotide polymorphism. On the contrary, FIGS. 12A and 12B and the accompanying text at col. 3, lines 31-42 demonstrate that while the disclosed chip can separate DNA fragments with about  $\geq 10$  base pairs size difference, it clearly would be unable to resolve DNA fragments of the same size with one or more base pair mismatches. In contrast to the

presently claimed chip, which uses two-dimensional or multidimensional electrophoresis combined with a stable thermal gradient to resolve minor nucleotide differences, Zhao only teaches one-dimensional electrophoresis. The Examiner's assertion that Zhao discloses "the possibility of multidimensional microchannels" (the OA at page 3) mischaracterizes the teachings of Zhao. FIG. 1 of Zhao shows a single microchannel **14** connected to two horizontal electrodes **28**. The vertical electrodes are not connected to a microchannel, and their purpose is not explained anywhere in the specification. Moreover, a careful reading of the specification at col. 10, lines 1-15 reveals that the term "multidimensional" at col. 10, lines 14-15 refers to "devices" and not to "microchannels". Thus, it is apparent that Zhao only teaches a one-dimensional microchannel that would be inherently unable to detect a nucleotide polymorphism or a single nucleotide polymorphism. Finally, Zhao does not teach anywhere in the specification the idea of using heating elements to establish a stable thermal gradient – it only teaches that the heating elements are used to "control the temperature" of the microchannel or a specific fragment thereof.

Thus, Applicants maintain that Zhao does not teach a capillary electrophoresis chip for detecting a nucleotide polymorphism or a single nucleotide polymorphism, comprising an upper channel layer comprising a two-dimensional or multidimensional microfluid channel and a lower heating layer capable of providing a stable temperature gradient for electrophoresis comprising two or more sets of temperature control elements that are spaced apart from each other. Since Zhao fails to expressly teach each and every limitation of the claimed invention, the strict identity standard for anticipation under 35 U.S.C. § 102(e) is not satisfied. Accordingly, Applicants respectfully submit that this rejection should be withdrawn.

### **Rejections under 35 U.S.C. § 103**

#### ***Obviousness over Zhao in View of Kaltenbach***

Claims 1-3 and 6-7 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Zhao *et al.* (US 6,939,451 B2, hereinafter "Zhao") in view of Kaltenbach *et al.* (EP 0,770,871 A3, listed in IDS, hereinafter "Kaltenbach").

The Examiner took the position that the heating layer of Zhao would be capable of providing a stable temperature gradient. Alternatively, the Examiner cited Kaltenbach for its alleged teaching of a capillary electrophoresis chip comprising a miniaturized column device and a lower heating layer comprising heating elements that are in thermal contact with the middle layer and can be independently set to different temperatures, thereby producing a temperature gradient across the middle layer for increasing sample processing efficiency (the OA at pages 4-5). The Examiner then concluded that it would have been obvious to one with ordinary skill in the art at the time of the invention to have the heaters comprising the lower heating layer of Zhao be independently set to different temperatures to produce a stable temperature gradient, as taught by Kaltenbach, because a temperature gradient can improve the microfluidic chip by increasing sample processing efficiency. Applicants respectfully traverse this rejection.

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). To establish a prima facie case of obviousness a three-prong test must be met. First, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference to achieve the claimed invention. *KSR* at 1731. And third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

“Rejections on obviousness grounds cannot be sustained by mere conclusory statements.” *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2007) (citations omitted). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Evidence of an unobvious or unexpected advantageous property can rebut prima facie obviousness. MPEP § 716.02(a). Moreover, if a proposed modification changes the principle of operation of a reference, the teachings of that reference are not

sufficient to render the claimed invention obvious. MPEP § 2143.01.VI, citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (emphasis added).

The teachings of Zhao have been discussed in detail above. Kaltenbach teaches a miniaturized planar column device comprising a thermal controller for regulating temperature, preferably a thermoelectric device comprising Peltier elements (abstract). Kaltenbach further teaches that the thermal controller may be used to provide temperature regulation over the entire surface of the column device, to provide regional temperature regulation, or to provide temperature regulation in such a manner as to generate a temperature gradient along the length of the miniaturized column device (col. 3, line 57 – col. 4, line 3; col. 25, lines 7-49).

Nevertheless, Kaltenbach suffers from the same fatal flaw as Zhao, namely, it only teaches a capillary chip device for one-dimensional electrophoresis. There is nothing in Kaltenbach teaching or suggesting using the disclosed capillary chip device for two-dimensional or multidimensional separation, as disclosed in the present invention. On the contrary, every single embodiment disclosed in Kaltenbach describes devices wherein sample separation is achieved by a unidirectional movement of the sample along a microchannel formed between two adjacent planar surfaces by laser ablation or another suitable technique.

The case law clearly states that if a proposed modification changes the principle of operation of a reference, the teachings of that reference do not render the claimed invention obvious (*In re Ratti*, 270 F.2d 810 (CCPA 1959)). Any person skilled in the art at the time of the present invention would recognize that a two-dimensional or multidimensional electrophoresis is conceptually different from a one-dimensional electrophoresis in that it permits a much higher level of sample resolution. The difference is not merely quantitative – it is qualitative. As explained in the specification at paragraph [0015] and in Figure 7, the presently claimed two-dimensional or multi-dimensional capillary electrophoresis device, combined with a stable thermal gradient, permits separation of two nucleotide molecules of the same size that have as little as one mismatched base pair, thus allowing detection of a nucleotide polymorphism or a single nucleotide polymorphism. None of the devices disclosed in Zhao or Kaltenbach have the same level of resolution, which is the

reason why neither reference teaches or even suggests detection of a nucleotide polymorphism or a single nucleotide polymorphism using such one-dimensional electrophoresis devices.

Thus, Applicants respectfully submit that neither of the cited references, alone or in combination, teaches or suggests a capillary electrophoresis chip for detecting a nucleotide polymorphism or a single nucleotide polymorphism, comprising an upper channel layer comprising a two-dimensional or multidimensional microfluid channel. In the absence of a teaching or suggestion of each and every claim element, the cited combination fails to provide the motivation to practice the presently claimed invention. Moreover, by introducing an additional electrophoretic dimension(s), the present invention has altered the fundamental principle of operation of the cited references, effectively rebutting the obviousness argument. Therefore, the Office has failed to make a *prima facie* case of obviousness and this rejection under 35 U.S.C. § 103(a) should be withdrawn.

*Obviousness over Zhao in View of Kaltenbach, Further in View of Hodes*

Claim 4 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Zhao, or alternatively Zhao in view of Kaltenbach, as applied to claim 1 above, and further in view of Hodes (US 3,502,558, hereinafter “Hodes”).

The Examiner alleged that Zhao discloses that the specific design and composition of the driving electrodes on the middle cover layer should be understood by those skilled in the art to be electrically conductive, but does not disclose the specific examples used in electrodes that are electrically conductive. To cure that deficiency of Zhao, the Examiner cited Hodes, which allegedly discloses a method of depositing gelatin on electrodes made of electrically conductive material such as gold, platinum or graphite. The Examiner then concluded that it would have been obvious to one with ordinary skill in the art at the time of the invention to have the integrated electrodes of the middle layer made of electrically conductive material such as gold, platinum or graphite in the invention of Zhao because Zhao already provides electrodes and as taught by Hodes the suitable electrode material can be any of gold, platinum or graphite because they are electrically conductive (the OA at pages 5-6).

Applicants respectfully traverse this rejection for substantially the same reasons as those set forth above. The teachings of Zhao and Kaltenbach have been discussed in detail above. Hodes merely teaches that gold, platinum or graphite can be used as electrically conductive materials. Much like Zhao and Kaltenbach, Hodes does not teach an upper channel layer comprising a two-dimensional or multidimensional microfluid channel. As such, Hodes fails to cure the deficiencies of Zhao and Kaltenbach discussed above.

Thus, none of the cited references, alone or in combination, teaches or suggests a capillary electrophoresis chip for detecting a nucleotide polymorphism or a single nucleotide polymorphism, comprising an upper channel layer comprising a two-dimensional or multidimensional microfluid channel. In the absence of a teaching or suggestion of each and every claim element, the cited combination fails to provide the motivation to practice the presently claimed invention. Moreover, by introducing an additional electrophoretic dimension(s), the present invention has altered the fundamental principle of operation of the cited references, effectively rebutting the obviousness argument. Therefore, the Office has failed to make a *prima facie* case of obviousness and this rejection under 35 U.S.C. § 103(a) should be withdrawn.

*Obviousness over Zhao in View of Kaltenbach, Further in View of Johnck*

Claim 5 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Zhao, or alternatively Zhao in view of Kaltenbach, as applied to claim 1 above, and further in view of Johnck *et al.* (US 200310161572 A1, hereinafter “Johnck”).

The Examiner alleged that Zhao discloses that the middle cover layer can be coated with a pressure sensitive adhesive which is then pressed against the substrate containing channels and wells, but does not disclose the specific examples of pressure sensitive adhesives that can be used to coat the middle cover layer. To cure that deficiency of Zhao, the Examiner cited Johnck, which allegedly discloses a microfluidic analysis system consisting of an upper substrate layer and a middle cover layer with thin-film electrodes integrated thereon, said cover layer coated with polydimethylsiloxane (PDMS) for insulating the exposed electrodes. The Examiner then concluded

that it would have been obvious to one with ordinary skill in the art at the time of the invention to have the middle cover layer with integrated electrode components be coated with PDMS in the invention of Zhao because Zhao already provides a coating layer for the cover layer and as taught by Johnck the PDMS coating can electrically insulate the electrodes (the OA at pages 6-7).

Applicants respectfully traverse this rejection for substantially the same reasons as those set forth above. The teachings of Zhao and Kaltenbach have been discussed in detail above. Johnck merely teaches that polydimethylsiloxane (PDMS) can be used for insulating electrodes. Much like Zhao and Kaltenbach, Johnck does not teach an upper channel layer comprising a two-dimensional or multidimensional microfluid channel. As such, Johnck fails to cure the deficiencies of Zhao and Kaltenbach discussed above.

Thus, none of the cited references, alone or in combination, teaches or suggests a capillary electrophoresis chip for detecting a nucleotide polymorphism or a single nucleotide polymorphism, comprising an upper channel layer comprising a two-dimensional or multidimensional microfluid channel. In the absence of a teaching or suggestion of each and every claim element, the cited combination fails to provide the motivation to practice the presently claimed invention. Moreover, by introducing an additional electrophoretic dimension(s), the present invention has altered the fundamental principle of operation of the cited references, effectively rebutting the obviousness argument. Therefore, the Office has failed to make a *prima facie* case of obviousness and this rejection under 35 U.S.C. § 103(a) should be withdrawn.



**CONCLUSION**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **docket No. 514572002400**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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